Remarks/Arguments

Reconsideration of the above-identified application in view of the present amendment is respectfully requested. By the present amendment claims 25, 33, and 40 have been amended to recite that the administration of the antibody does not decrease factor B levels in the blood. Support for this limitation can be found in the examples and particularly in examples 2-6 of the specification, which describe the administration of the antibody to sera and blood. In these examples, the antibody blocked complement activation but did not affect the amount of factor B in the blood and sera. This limitation is additionally supported by the fact that the antibody functions by binding to factor B in a manner that blocks factor B binding to properdin bound C3b and does not present synthesis is of factor B. The anti-factor B antibody does not lower level of factor B in the blood because it merely inhibits binding of factor B to properdin bound C3b. Claim 33 has also been amended to recite a method of treating disease pathologies associated with complement activation mediated by factor B. Support for this limitation can be found in claim 38, which has been cancelled. New claim 45 has been added to the application. New claim 45 recites that the anti-factor B antibody in an in vitro assay prevents factor B binding to C3b and properdin-bound C3b; prevents the formation of Bb, reduces C3a, *C5a,* and C5b-9 generation, reduces C3 conversion into C3a and C3b; reduces *C5* conversion into C5a and C5b, reducing the activation of neutrophils, monocytes and platelets, and inactivates cells bearing C3a and C5a receptors.

1. 35 U.S.C. §102 rejection of claims 25-27, 29-34, and 36-44

Claims 25-27, 29-34, and 36-44 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 00/021559 (Music Foundation for Research Development) (hereinafter, 'the '559 document"). The Office Action argues that the '559 document discloses that Factor B is a component of the alternative complement pathway, is a B cell growth factor, stimulates mononuclear cell cytoxicity, includes macrophage spreading, and solubilizes immune complexes. The Office Action also argues the '559 document discloses that factor B is an important mediator of complement mediated disease, treatment of subjects in need thereof with anti-factor B antibodies, the manufacture of monoclonal antibodies to factor B, the injection of an anti-factor B antibody to a subject, and the treatment of various diseases.

Claim 25, as discussed above, was amended to recite that administration of the antibody does not decrease factor B levels in the blood. Claim 25 is patentable over the '559 document because: (1) the '559 document fails to teach an anti-factor B antibody that prevents factor B binding to C3b and properdin-bound C3b; prevents the formation of Bb; reduces C3a, *C5a*, and C5b-9 generation; reduces C3 conversion into C3a and C3b; reduces *C5* conversion into C5a and C5b; reduces the activation of neutrophils, monocytes and platelets; and/or inactivates cells bearing C3a and C5a receptors, wherein the antibody does not decrease factor B levels in the blood; and (2) the '559 document does not provide an enabling disclosure of subject matter of claim 25.

1. The '559 document fails to teach an anti-factor B antibody that prevents factor B binding to C3b and properdin-bound C3b; prevents the formation of Bb; reduces C3a, *C5a*, and C5b-9 generation; reduces C3 conversion into C3a and C3b; reduces *C5* conversion into C5a and C5b; reduces the activation of neutrophils, monocytes and platelets; and/or inactivates cells bearing C3a and C5a receptors, wherein the antibody does not decrease factor B levels in the blood.

The '559 document teaches compositions and methods of treating or preventing factor-B mediated immune disease in a subject by administering to a subject an inhibitor of the synthesis or activity of factor B. (Page 2, lines 31; page 3, lines 1-3). In the examples and the description of the '559 document, the compositions inhibit serum levels of factor B or "activity" of factor B. The '559 document notes on page 10 and page 11 that a higher than normal level of Factor B indicates complement-mediated immune disease and active inflammation. (Page 10, lines 29-30; page 11, lines 12-13).

To treat complement mediated immune disease, which is associated with a higher level of Factor B, the '559 document teaches administering an antibody to Factor B that reduces the serum level or activity of factor B, thereby reducing the amount of Factor B available to begin the cascade of events in the alternative complement pathway, which enhances activation of the classical pathway. (Emphasis added) (Page 6, lines 15-18). The '559 document also notes that the dosage of factor B antibody administered to the subject would be based on that amount of antibody necessary to eliminate Factor B from the serum and the activity of factor B in the serum (Page 20, lines 29-31) and that the efficacy of the antibody can be measured by

> "a fall in the serum level of Factor B and a rise in the serum levels of C3 and C4, as well as a decrease in the amount of protein excreted in the urine of the

> subject, indicate that the antibody has bound to Factor and B and eliminated the activity of Factor B in the complement system." (Page 7, lines 27-30).

The '559 document, however, provides little, if any teachings, about the anti-factor B antibody. Specifically, the '559 document does not disclose (1) the identity of the antibody, (2) the structure or amino acid sequence of the antibody, or (3) the amino acid sequence of an immunogenic epitope that can be used to form the antibody. Factor B is a large protein that can produce a vast number of antibodies that can bind to many of the antigenic and functional sites of factor B. Most of the antibodies to factor B would not inhibit the alternative complement pathway. The only teaching provided by the '559 document that can be used to identify the antibody is that the antibody reduces factor B serum levels available to begin activation of the alternative complement pathway. (Page 6, lines 15-19). One skilled in the art can therefore only envision from the teachings of the '559 document an anti-factor B antibody that binds to factor B and reduces serum factor B levels, i.e., an anti-factor B antibody that can be selected or identified by determining if the antibody reduces factor B serum levels. In other words, the '559 document only teaches an anti-factor B antibody that decreases factor B serum levels.

Claim 25, as discussed above, was amended to recite that the administration of the anti-factor B antibody to the subject does not decrease factor B levels in the blood. The '559 document only teaches administering an anti-factor B antibody that decreases factor B serum levels and fails to teach an anti-factor B antibody that does not decrease the level of factor B in the blood while preventing factor B binding to C3b and properdin-bound C3b; preventing the formation of Bb; reducing C3a, *C5a,* and C5b-9 generation; reducing C3 conversion into C3a and C3b; reducing *C5*

conversion into C5a and C5b; reducing the activation of neutrophils, monocytes and platelets; and/or inactivating cells bearing C3a and C5a receptors.

Moreover, the mechanism of action of the anti-factor B antibody recited in the present application and claim 25 is to inhibit functional activity of Factor B, without altering the levels of factor B. This is advantageous as it allows Factor B to participate in other roles. As noted on page 2 of the '559 document, Factor B functions as a cell growth factor, in mononuclear cell toxicity, marcrophage spreading and in generation of immune complexes. Thus, the anti-factor B antibody of claim 25 will inhibit the alternate complement pathway but still allow other factor B functions, such as a cell growth factor, in mononuclear toxicity, etc.

Additionally, the serum or blood levels in a subject treated with anti-factor B antibody of claim 25 will remain unchanged or potentially increase, but serum levels of C3a, C5a, and C5b-9 will be reduced as shown in the examples. Serum factor B levels in patients with complement mediated diseases is typically lower than normal healthy controls. This is because the factor B that is produced is consumed by elevated activation of the alternative complement pathway. Thus, factor B synthesis is increased in parallel with increased complement activation and factor B consumption (i.e., increased turnover of factor B). The anti-factor B antibody of claim 25 will therefore elevate factor B levels toward those observed in normal healthy control subjects rather than decrease the factor B levels.

In contrast, the mechanism of action of the Factor B antibody taught in the '559 document will not only prevent complement activation, but also block all functions of Factor B. Removal of factor B will not only effect its functions in the

complement pathway, but also affect its function as a cell growth factor, in mononuclear toxicity, etc. Moreover, as noted on page 7, lines 27 and 28 of the '559 document, the anti-factor B antibody will decrease factor B levels and increase C3 levels, which is contrast to anti-factor B antibody recited in claim 25.

Thus, the '559 document only teaches antibodies that decrease factor B serum levels, increase C3 levels, affect all the functions of factor B and teach away from an anti-factor antibody that prevents factor B binding to C3b and properdin-bound C3b; prevents the formation of Bb; reduces C3a, *C5a,* and C5b-9 generation; reduces C3 conversion into C3a and C3b; reduces *C5* conversion into C5a and C5b; reduces the activation of neutrophils, monocytes and platelets; and/or inactivates cells bearing C3a and C5a receptors without decreasing factor B levels in the blood.

2. The '559 document does not provide an enabling disclosure of the subject matter of claim 25.

The development of antibodies that target Factor B to prevent a specific function of factor B, in this case complement activation functions, is not trivial. As discussed above, factor B is a large protein that can produce large numbers of antibodies that bind many different antigenic and functional sites of factor B. Many antibodies have been developed that bind to factor B. Most do not block factor B's ability to inhibit activation of the complement pathway. Antibodies that block the function of factor B to activate complement require the ability to bind to specific sites on the factor B protein.

The '559 document provides no teaching that would allow one skilled in the art to produce an anti-factor B antibody that prevents factor B binding to C3b and properdin-bound C3b; prevents the formation of Bb; reduces C3a, *C5a,* and C5b-9

generation; reduces C3 conversion into C3a and C3b; reduces *C5* conversion into C5a and C5b; reduces the activation of neutrophils, monocytes and platelets; and/or inactivates cells bearing C3a and C5a receptors without undue experimentation. The '559 document does not disclose an antibody that will prevent complement activation nor does the '559 document provide any teaching on specific epitopes that can be used to generate antibodies that inhibit complement activity. There is no disclosure in the '559 document of any potential binding sequences as well how such antibodies could be potentially screened other than to indicate that the antibodies can reduce factor B serum levels. Those skilled in the art can make monoclonal antibodies to factor B; however, selection of disease relevant antibodies that inhibit alternative pathway activation would require undue experimentation without a disclosure of specific assay systems required for such selection. No such assays are taught or suggested by the '559 document. Thus, one skilled in the art cannot envision which antibodies are being taught by the '559 document let alone envision an anti-factor B antibody that prevents factor B binding to C3b and properdin-bound C3b; prevents the formation of Bb; reduces C3a, *C5a,* and C5b-9 generation; reduces C3 conversion into C3a and C3b; reduces *C5* conversion into C5a and C5b; reduces the activation of neutrophils, monocytes and platelets; and/or inactivates cells bearing C3a and C5a receptors, without decreasing factor B serum levels.

Additionally, the '559 document provides methods which teach that blocking factor B production reduce formation and deposition of immune complexes and thus, disease pathology. It is difficult to envision antibodies that will reduce the serum

levels of Factor B or prevent Factor B synthesis. The '559 document does not address which antibodies are claimed, nor does the invention address how these antibodies will prevent Factor B synthesis or activity.

Without a disclosure enabling one skilled in the art to identify monoclonal antibodies that reduce serum levels or activity without undue experimentation, the '559 document is not applicable as prior art. (See Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Reserch, 346 F.3d 1051, 1054,68 USPQ2d 1372, 1376 (Fed. Cir. 2003)). Accordingly, withdrawal of rejection of claim 25 is respectfully requested .

Claims 26-27 and 29-32 depend directly or indirectly from claim 25 and are allowable because of the aforementioned deficiencies recited with respect to claim 25 and because of the specific limitations recited in claim 25.

Claim 33 includes similar limitations as claim 25 except recites a method of treating disease pathologies associated with complement activation and that the anti-factor B antibody in an in vitro assay prevents factor B binding to C3b and properdin-bound C3b; prevents the formation of Bb; reduces C3a, *C5a,* and C5b-9 generation; reduces C3 conversion into C3a and C3b; reduces *C5* conversion into C5a and C5b; reduces the activation of neutrophils, monocytes and platelets; and inactivates cells bearing C3a and C5a receptors. Claim 25 is patentable over the '559 document because of the aforementioned deficiencies in the rejection mentioned above with respect to claim 25.

Claim 33 is also patentable over the '559 document because the '559 document does not teach anti-factor B antibody in an in vitro assay prevents factor B binding to C3b and properdin-bound C3b; prevents the formation of Bb; reduces

C3a, *C5a,* and C5b-9 generation; reduces C3 conversion into C3a and C3b; reduces *C5* conversion into C5a and C5b; reduces the activation of neutrophils, monocytes and platelets; and inactivates cells bearing C3a and C5a receptors.

The '559 document as discussed above does not teach the mechanism of action of the anti-factor B antibody. The '559 document teaches only antibodies that decrease factor B serum levels and teach away from an anti-factor antibody that has all of the following features: prevents factor B binding to C3b and properdin-bound C3b; prevents the formation of Bb; reduces C3a, *C5a,* and C5b-9 generation; reduces C3 conversion into C3a and C3b; reduces *C5* conversion into C5a and C5b; reduces the activation of neutrophils, monocytes and platelets; and inactivates cells bearing C3a and C5a receptors without decreasing factor B levels in the blood. Moreover, the '559 document neither teaches nor suggests any assay that would allow one skilled in the art to identify and/or use an anti-factor B antibody with such properties.

Additionally, the '559 document does not demonstrate that preventing synthesis of factor B reduces disease pathology by preventing complement activation. Other functions of factor B that impact disease processes could account for the observed effects of factor B gene deletion to reduce disease pathology. As an example, factor B alters macrophage and mononuclear cell functions. These cells produce cytokines that are known to impact B cell production of antibodies. One complication in mice in which a single gene is "knocked-out" is that other genes closely positioned to the deleted gene are often affected in such a manner that functions of the deleted gene/protein are assumed by another functionally related

gene/protein. Thus, deletion of one gene is compensated for by a closely related gene. In the case of the factor B gene, this could be by the gene for C2. Further, with gene knockout models, it is common for there to be functional redundancy in biological systems, such that other related proteins take over the role of Factor B in vivo. Examples of this are well known to one skilled in the art. The '559 document does not teach that disease reducing effects of deleting the factor B gene results from a lack of complement activation. Given the complex role of factor B, without experiments to demonstrate that the factor B knock-out mouse has no alternative pathway activity, or that lack of alternative pathway reduces disease pathology, one skilled in the art cannot conclude that preventing synthesis of factor B will inhibit alternative pathway activation and disease pathology in this mouse model. Thus, the '559 document teaches that complete removal of the factor B gene is required to prevent disease pathology. The model system does not teach that specifically inhibiting factor B function in activation of the alternative pathway prevents disease pathology. Accordingly, the '559 document fails to teach all of the limitations of claim 33 and allowance of claim 33 is respectfully requested.

Claims 34 and 36-37 and 39 depend directly or indirectly from claim 33 and are allowable because of the aforementioned deficiencies recited with respect to claim 33 and because of the specific limitations recited in claims 36-39.

Claim 40 recites a method of inhibiting complement alternative pathway activation associated with extracorporeal circulation inflammation. The method includes contacting factor B in blood of a subject going undergoing extra corporeal circulation with an antibody that specifically binds to factor B. The anti-factor

antibody in an *in vitro* assay preventing factor B binding to C3b and properdin-bound C3b, preventing the formation of Bb; reducing C3a, *C5a,* and C5b-9 generation in blood, reducing C3 conversion into C3a and C3b; reducing *C5* conversion into C5a and C5b; reducing the activation of neutrophils, monocytes and platelets and/or inactivating cells bearing C3a and C5a receptors, wherein administration of the antibody does not decrease factor B levels in the blood.

Claim 40 includes similar limitations as claim 25 and is therefore patentable over the '559 document because of the aforementioned deficiencies in the rejection mentioned above with respect to claim 25.

Claim 40 is also patentable over the '559 document because the '559 document does not teach contacting factor B in blood of a subject going undergoing extracorporeal circulation with an antibody that specifically binds to factor B. The '559 document make no mention of an extracorporeal circulation or that the antibody contacts factor B in blood during such procedure. Accordingly, the claim 40 is patentable over the '559 document and allowance of claim 40 is respectfully requested.

Claims 41-44 depend directly from claim 40 and are allowable because of the aforementioned deficiencies recited with respect to claim 40 and because of the specific limitations recited in claims 41-44.

2. 35 U.S.C. § 103 rejection of claims 28 and 35

Claims 28 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/21559 (Music Foundation for Research Development; N on form PTO-892, newly cited) as applied to claims 27 and 34 above, and further in view of Harlow

et al. (Antibodies: A laboratory Manual. [1988] pages 72-77, 92-97, 128-135, 141-157 and 628-631.

Claims 28 and 35 depend directly or indirectly from claims 25 and 33 and are allowable because of the aforementioned deficiencies recited with respect to claim 25 and 33 and because of the specific limitations recited in claims 28 and 35.

In view of the foregoing, it is respectfully submitted that the above-identified application is in condition for allowance, and allowance of the above-identified application is respectfully requested.

Please charge any deficiency or credit any overpayment in the fees for this amendment to our Deposit Account No. 20-0090.

Respectfully submitted,

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